# JaCVAM update

June 17, 2011

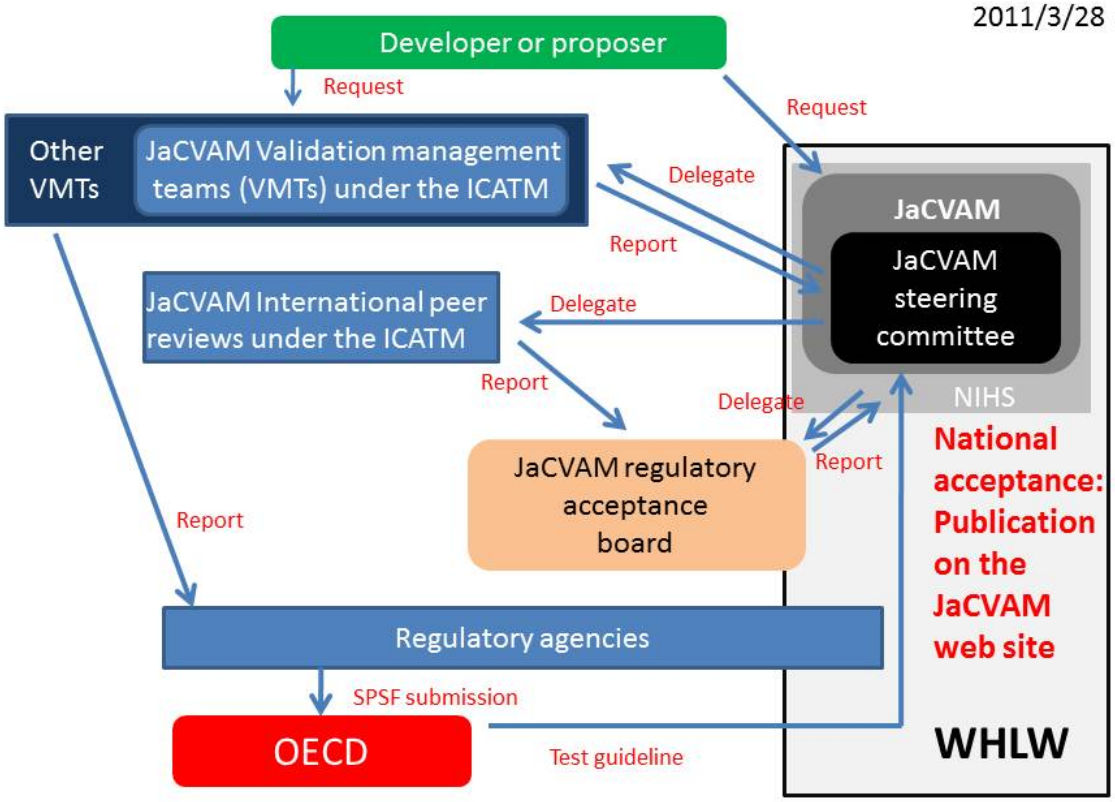
NICEATM

# Present status on Regulatory Acceptance of Alternatives for Animal Testing in Japan

In 1986, it was notified the alternative method adopted by OECD or regarded as relevant as the one adopted OECD, the data obtained by such testing methods have been used for the submission for quasi-drug application, or for application of an ingredient for the inclusion to Cosmetic Standard.

In February 2011, MHLW notified that data obtained in alternative testing method approved by JaCVAM Steering Committee can be used for the submission for quasi-drug application, or for application of an ingredient for the inclusion of Cosmetic Standard.

2011/3/28 draft




Regulatory acceptance system on new or revised test methods for quasi drug and/or cosmetic products in Japan

# Accepted methods by the JaCVAM regulatory acceptance board

- The Bovine Corneal Opacity and Permeability (BCOP) Test Method for Identifying Ocular Corrosives and Severe Irritants
- The Isolated Chicken Eye (ICE) for Identifying Ocular Corrosives and Severe Irritants
- Skin sensitization assay, LLNA：DA
- Skin sensitization assay, LLNA：BrdU-ELISA
- *In vitro* skin irritation testing: EPISKIN
- *In vitro* skin corrosion testing: Vitrolife-Skin, EpiDerm
- *In vitro* cytotoxicity test methods for estimating starting doses for acute oral systemic toxicity tests

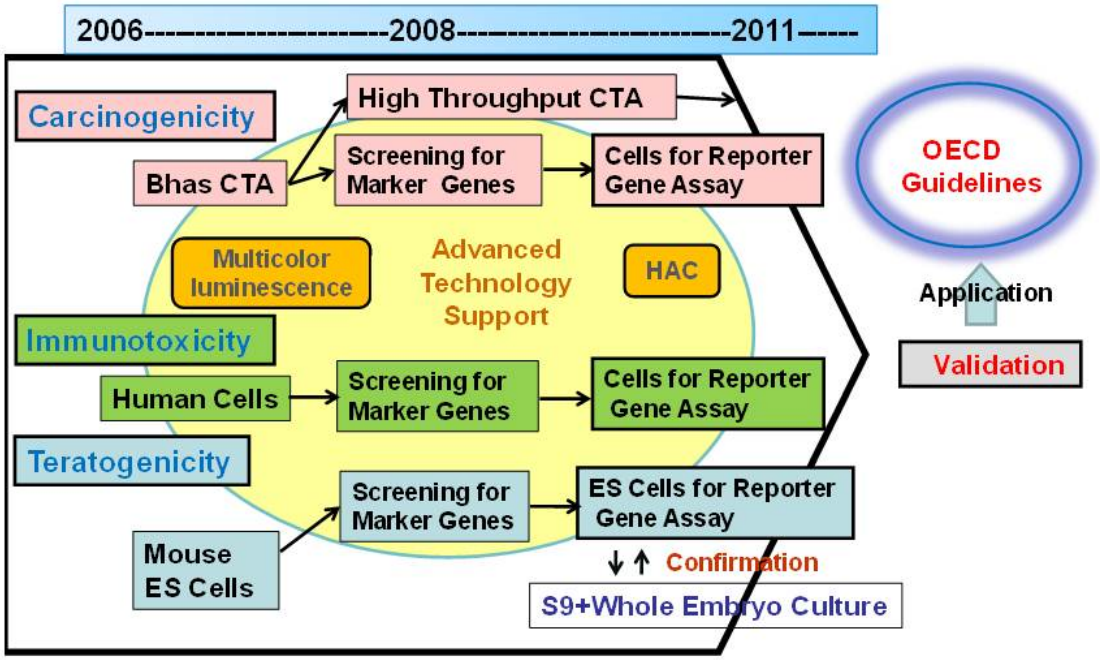
# On-going of National or International peer review

- SHE & 3T3 assays for cell transformation assay (with ECVAM)
- Bhas cell transformation assay ( in preparation)
- LabCyte assay for skin irritation testing (with OECD)
- SIRC assay for eye irritation testing
- MATREX assay for eye irritation testing
- Short time exposure assay for eye irritation testing ( in preparation with ICCVAM)

# On-going of validation study

- h-CLAT assay for skin sensitization testing (ECVAM/JaCVAM)
- *In vivo/in vitro* Comet assay for genotoxicity testing (JaCVAM/ICCVAM/ECVAM/KoCVAM)
- Stably Transfected Transcriptional Activation (STTA) antagonist assay for endocrine disruptor screening (JaCVAM/OECD VMG-NA)
- ROS assay for phototoxicity testing (ECVAM/JaCVAM, in preparation)

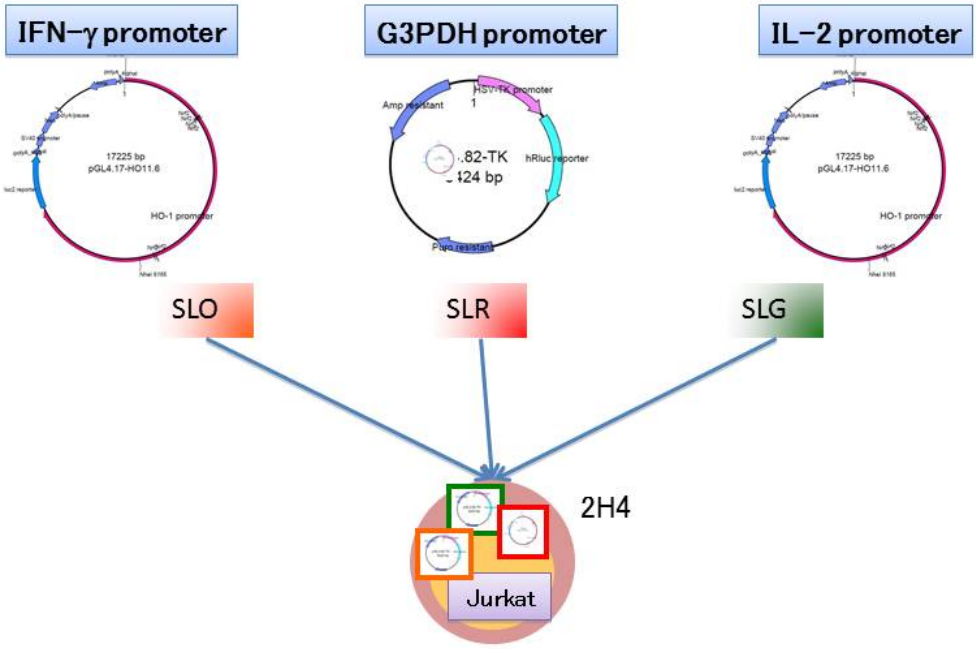
## Development of High Throghput Toxicity Test Systems on Carcinogenicity, Teratogenicity and Immunotoxicity



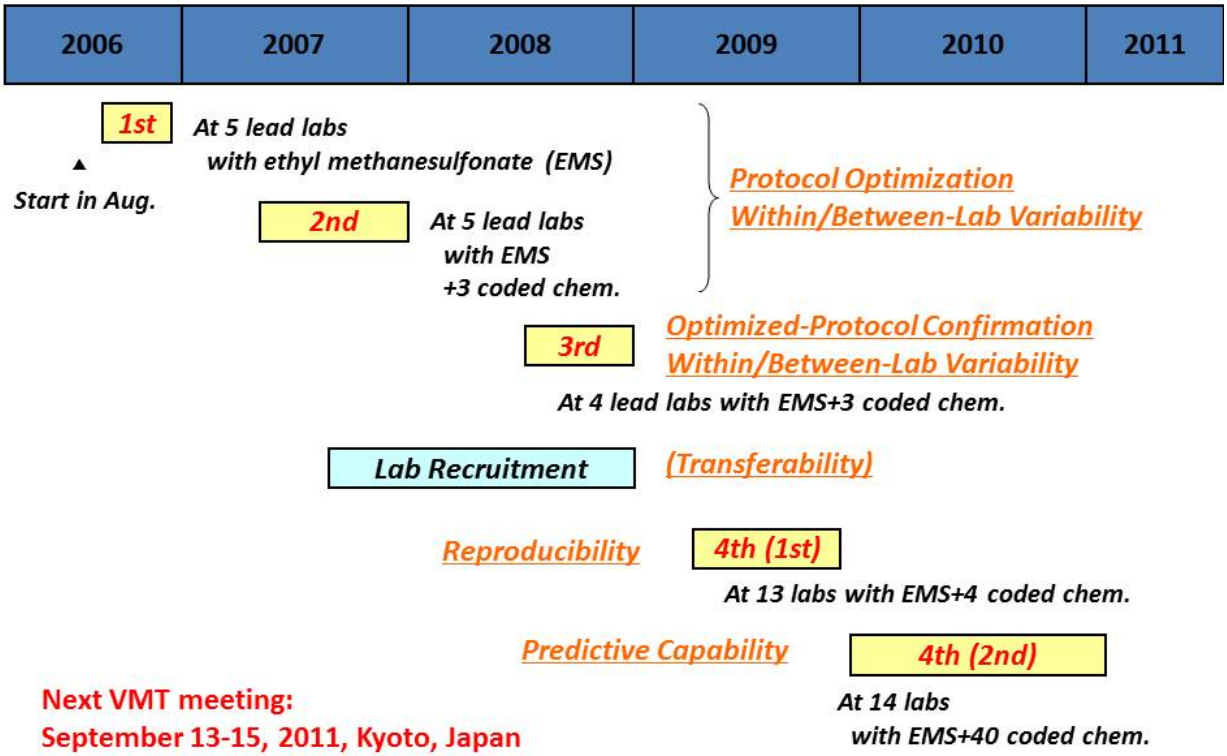
# *In vitro* immunotoxicity assay

This autumn,  we will start the validation studies in this field

I hope you will recommend us a liaison of ICCVAM as the VMT member.



# History of Our Validation Effort (In Vivo comet assay )

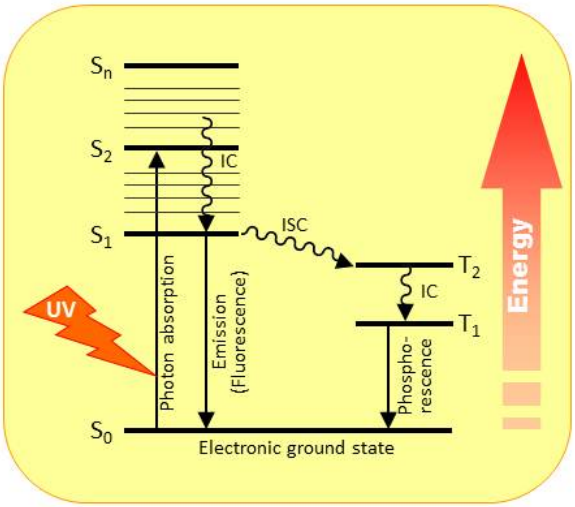


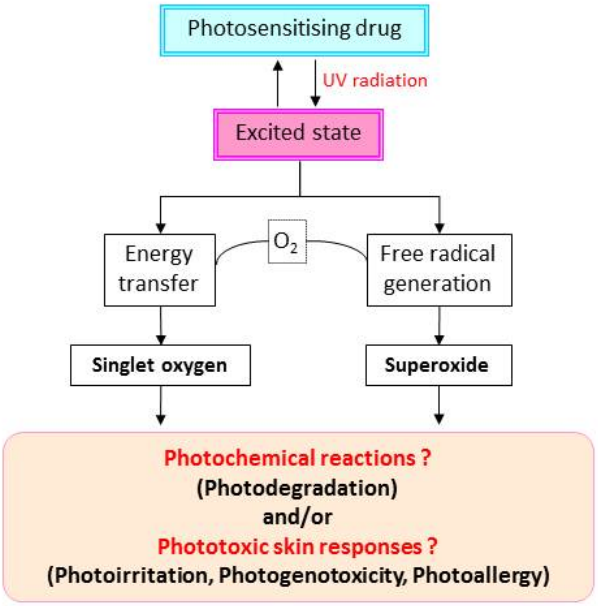

**Next VMT meeting:**
**September 13-15, 2011, Kyoto, Japan**

# Possible phototoxic pathways

- Working hypothesis;

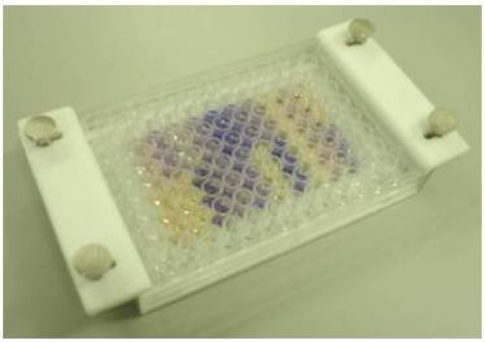
*"ROS may induce photochemical/toxic reactions"*

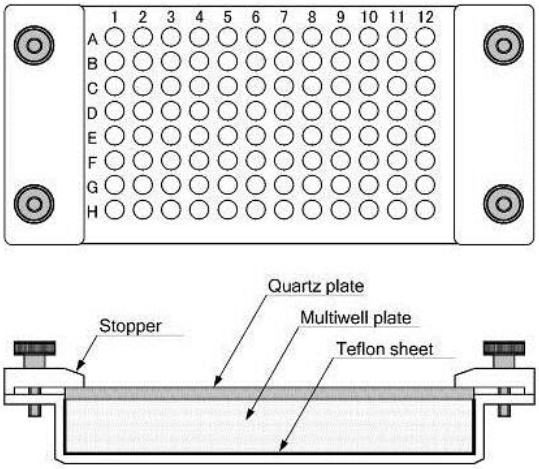


# High throughput ROS assay

◆Quartz reaction container for multiwell assay






◆ Solar simulator

Overnight assay (18 hr):

LTX-01 (Xe lamp, 18 W/m$^2$; Nagano Science)

Short-time assay (1 hr) :

Suntest CPS (Xe lamp, 250 W/m$^2$; Atlas)

Onoue S *et al.*, *J Pharm Biomed Anal* **46** (2008) 187-193.
Onoue S *et al.*, *Pharm Res* **25** (2008) 861-868

# Schedule for ROS assay validation study

| Month | Activity |
|---|---|
| January, 2011 | Selection of participating research laboratories |
| | Establish the VMT |
| | Election and approval of the *Trial Coordinator* and each group |
| | Deliberation, decision and read-through of draft study plan |
| | Deliberation and decision of study protocol |
| | Preparation of a tentative list of test chemicals |
| March, 2011 | Distribution of test chemicals, standard chemicals and positive control chemicals |
| | Start of 1st phase study |
| May, 2011 | End of 1st phase study |
| | VMT Meeting /Outline of study results |
| June, 2011 | VMT Meeting |
| | Chemical selection for 2nd phase study |
| July, 2011 | Coding and distribution of coded test chemicals, standard chemicals and positive control chemicals |
| August, 2011 | Start of 2nd phase study |
| October, 2011 | Start of 2nd phase study |
| December, 2011 | Preparation, deliberation and decision of draft study report |

# Transferability of ROS assay by 1 st phase validation study

| Compound | Tanabe Mitsubishi Pharma | Univ. of Shizuoka | FDSC |
|---|---|---|---|
| 5-Fluorouracil (5-FU) | N | N | N |
| 8-Methoxy psoralen (8-MOP) | P | P | P |
| Amiodarone | P | P | P |
| Chlorpromazine | P | P | P |
| Diclofenac | P | P | P |
| Doxycycline | P | P | P |
| Furosemide | P | P | P |
| Ketoprofen | P | P | P |
| Levofloxacin | P | P | P |
| Norfloxacin | P | P | P |
| Omeprazole | P | P | P |
| Quinine | P | P | P |
| Sulisobenzone | N | N | N |

# New projects in Japan

- Research and Development of Internationally Leading Hazard Assessment and Test Methods Essential for the New Chemical Management Policy
- Agri-Health Translational Research Project

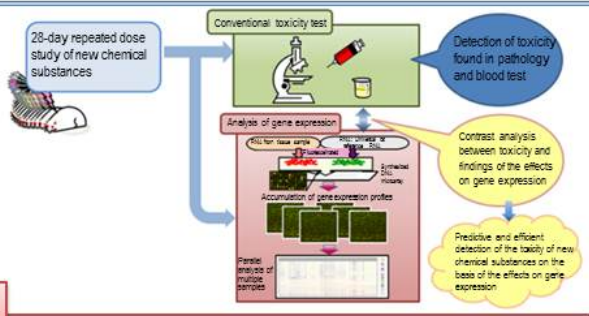
Contents of project (1) (Development of methods to obtain data on the possibility of the expression of toxicity on the basis of altered gene expression)

## Targets of the project

To aim at analyzing changes in gene expression in animals tested in *in vivo* 28-day repeated dose studies and establishing methods that can predict and efficiently detect the effects of chemical substances in major organs and the presence of carcinogenicity, immunotoxicity, etc.

***○Contents of the projects***

Establishing and standardizing methods to obtain data by analyzing the correlation between *in vivo* responses and changes in gene expression in animals exposed to chemical substances of known toxicity, including carcinogenicity and immunotoxicity, etc., and publishing them




## Expected deliverables and their application

- Establishing datasets of carcinogenicity and immunotoxicity and changes in gene expression
- In rats, 28-day repeated dose studies are conducted and changes in gene expression are analyzed. By comparing the analyzed data with the datasets obtained from the project and validating them, carcinogenicity and immunotoxicity can be predicted and efficiently assessed.
- Application to the risk assessment of new chemical substances in the Chemical Substances Control Law (CSCL) (the total number of new chemical substances that were planned to be manufactured or imported over 1 ton per annum were notified 666 in 2008).

Contents of project (2) (Development of cell assays to detect toxicities, including target organ toxicity and metabolic function)

**Targets of the project**

To aim at establishing in vitro test methods to speedily and efficiently assess the endpoints of 28-day repeated dose toxicities (hepatotoxicity, nephrotoxicity, etc.)

***Contents of the projects***

Detecting genes related to toxicities including 28-day repeated toxicity (hepatotoxicity, nephrotoxicity, etc.) and developing cultured cells where these toxicities are detected

Search for genes related to toxicity

Cultured cells where toxicities including 28-day repeated dose toxicity (hepatotoxicity, nephrotoxicity, etc.) can be detected

Introduction of genes related to toxicity, etc.

Cultured cell

**Expected deliverables and their application**

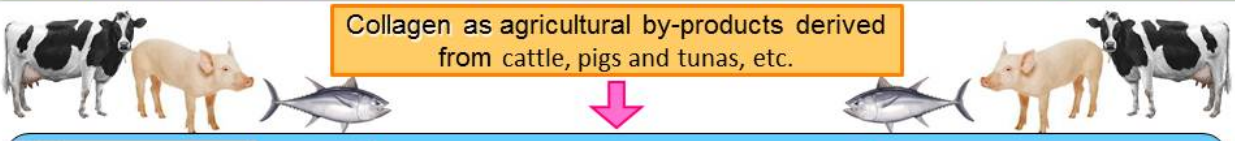
- Developing cells and establishing assessment methods that can speedily and efficiently assess 28-day repeated dose toxicities (hepatotoxicity, nephrotoxicity, etc.)
- By applying the chemical substance to the cells developed in the project, 28-repeated dose toxicity, etc., can be assessed.

➢ Application to the risk assessment of substances of known toxicity in the CSCL (about 20,000 substances), etc.

**Agri-Health Translational Research Project** (Ministry of Agriculture, Forestry and Fisheries, Japan)

**"Development of novel biomedical devices using animal-derived byproducts (Vitrigel Project)"**

**Project Leader: Toshiaki Takezawa, Ph. D.** (Senior Researcher, National Institute of Agrobiological Sciences)



Collagen as agricultural by-products derived from cattle, pigs and tunas, etc.

## Development of novel collagen vitrigels

Development of atelocollagen vitrigel membranes useful for regenerative medicine

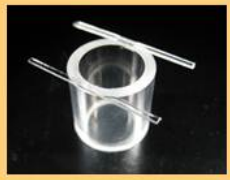
↓

GOAL: Application for clinical trial

Development of collagen vitrigel chambers useful for the researches in drug discovery and alternatives to animal experiments

↓

GOAL: Reconstruction of "tissue sheet" type- and "organoid plate" type-culture models useful for ADMET (absorption, distribution, metabolism, excretion and toxicity) analyses of chemicals



### Development of technologies for regenerative medine

- Development of artificial skin
- Development of artificial cornea
- Development of artificial trachea

↓

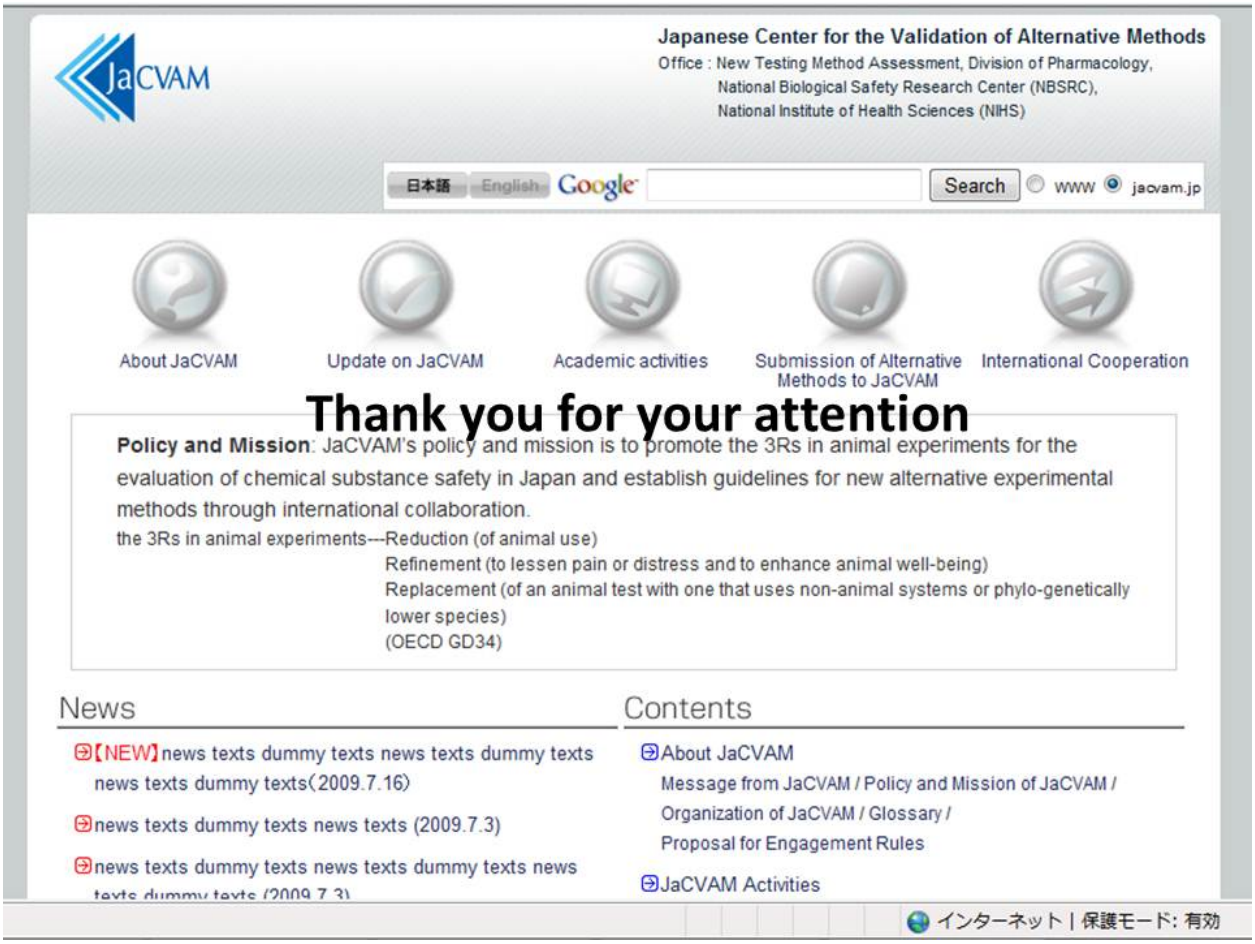
GOAL: Application for clinical trial

### Development of culture systems for alternative to animal testing

- Development of skin sensitization test
- Development of eye irritation test

↓

GOAL: Pre-validation of developed tests


JaCVAM
Japanese Center for the Validation of Alternative Methods
Office : New Testing Method Assessment, Division of Pharmacology,
National Biological Safety Research Center (NBSRC),
National Institute of Health Sciences (NIHS)
日本語 English Google Search www jacvam.jp
About JaCVAM
Update on JaCVAM
Academic activities
Submission of Alternative Methods to JaCVAM
International Cooperation
Thank you for your attention
Policy and Mission: JaCVAM's policy and mission is to promote the 3Rs in animal experiments for the evaluation of chemical substance safety in Japan and establish guidelines for new alternative experimental methods through international collaboration.
the 3Rs in animal experiments---Reduction (of animal use)
Refinement (to lessen pain or distress and to enhance animal well-being)
Replacement (of an animal test with one that uses non-animal systems or phylo-genetically lower species)
(OECD GD34)
News
【NEW】news texts dummy texts news texts dummy texts news texts dummy texts〈2009.7.16〉
news texts dummy texts news texts (2009.7.3)
news texts dummy texts news texts dummy texts news texts dummy texts (2009.7.3)
Contents
About JaCVAM
Message from JaCVAM / Policy and Mission of JaCVAM / Organization of JaCVAM / Glossary / Proposal for Engagement Rules
JaCVAM Activities
インターネット | 保護モード: 有効